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Carbamazepine-Induced Thrombocytopenia Defined by a Challenge Test

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Carbamazepine (CBZ), a widely used anticonvulsant, occasionally causes serious hematologic disorders. A 12-year-old boy was admitted because of a diffuse petechial rash and profound thrombocytopenia (10×10^9 platelets/l), after having been treated for epilepsy with CBZ for 12 days. Seven days following withdrawal of CBZ and initiation of prednisolone therapy, the platelet count recovered. In a subsequent challenge test with CBZ, platelet counts again decreased, and the levels of platelet-associated IgG and serum interleukin-6 increased. No antibodies against platelet glycoprotein IIb/IIIa or Ib were detected in plasma. We believe that this is the first reported occasion when CBZ-induced thrombocytopenia has been defined by a rechallenge test. Am. J. Hematol. 64:52–55, 1999. © 1999 Wiley-Liss, Inc.

Key words: carbamazepine; thrombocytopenia; challenge test; platelet-associated IgG; interleukin-6

INTRODUCTION

Carbamazepine (CBZ) is widely used as an anticonvulsant because, given its effectiveness, it has a relatively low incidence of adverse effects. However, CBZ occasionally causes such hematologic disorders as aplastic anemia, thrombocytopenia, and leukopenia [1]. The prevalence of fatal aplastic anemia is slightly under 1 treated patients in 50,000, while persistent leukopenia occurs in 2% of patients treated with CBZ. In contrast, thrombocytopenia is distinctly uncommon. To our knowledge, only 23 cases of CBZ-induced thrombocytopenia have been reported since 1968; 17 patients are summarized in Table I [2–15] and hematological data were incompletely described for 6 patients [16]. The thrombocytopenia most often develops 2 weeks after initiation of CBZ treatment and recovers within 1 week after discontinuation of CBZ [11,13]. Some cases were asymptomatic and were unexpectedly found by routine laboratory testing [9,15]. Other cases showed fever, skin rashes, arthralgia, or swollen joints [14,16]. No study on a patient with CBZ-induced thrombocytopenia who underwent a subsequent challenge test with CBZ has previously been reported. We describe a patient with CBZ-induced thrombocytopenia defined after a resolved episode by a challenge test.

CASE REPORT

A 12-year-old boy was admitted to our hospital because of generalized petechiae and ecchymoses. The patient had been well until the age of 12 years, when a simple partial seizure occurred. He had no history of allergic diseases or viral infections such as those typically preceding idiopathic thrombocytopenic purpura. Treatment for the seizure was started 11 days before admission with 14 mg/kg/day (600 mg/day) of CBZ. He received no other medication. Eight days after beginning CBZ treatment, petechial rashes developed over the shoulders and became prominent. High fever and erythematous rashes occurred on the tenth day of CBZ.

On admission, diffuse petechiae and ecchymoses were seen. A complete blood count included a platelet count of 10×10^9/l; hemoglobin, 148 g/l; and a white blood cell

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TABLE I. Previous Cases of Carbamazepine-Induced Thrombocytopenia*

Age/gender (years)	CBZ (mg/d)	Duration[a]	Platelets (10^9/l)[b]	Megakaryocytes	Complication	Antibody	Therapy	Outcome	Refs
1. 79/F	800	10 mo.	50	Increased, immature			Stop	Recovered	2
2. 16/F	600	2 wk.	11				Stop	Recovered, 4 d.	3
3. 15/M	750	10 d.	2	Increased, immature		IgG	Stop	Recovered, 5 d.	4
4. 31/F	400	2 mo.	5	Increased, immature			Stop	Recovered, 1 wk.	5
5. 33/F	800	3 wk.	55		liver dysfunction fever, erythema		Stop, PSL	Recovered, 4 d.	6
6. 66/F	200	17 d.	5				Stop	Recovered, 1 wk.	7
7. 4/F	300	2 wk.	14				Stop	Recovered, 4 d.	8
8. 18/M	600	2 wk.	14				Stop	Recovered, 5 d.	9
9. 57/M	600	11 d.	11		malaise		Stop	Recovered	10
10. 20/M	600	2 wk.	13		fever		Stop	Recovered, 1 wk.	11
11. 18/F	600	2 wk.	27		leukopenia		Stop	Recovered, 1 wk.	11
12. 29/M	600	2 wk.	11				Stop	Recovered, 1 wk.	11
13. 47/M	600	2 wk.	10	Increased	fever		Stop	Recovered, 6 d.	11
14. 8/F	14/kg	2 wk.	6			N.D.	Stop	Recovered, 4 d.	12
15. 40/F	600	2 wk.	49				Stop	Recovered, 3 d.	13
16. 10/F	300	10 d.	6	Decreased	vasculitis		Stop, PSL PLT	Recovered, 4 d.	14
17. 20/F	400	2 wk.	69				None	Recovered, 1 wk.	15
[c] 12/M	14/kg	12 d.	10	Increased, immature	fever, erythema	N.D.	Stop, PSL	Recovered, 7 d.	

*PSL, prednisolone; N.D., not detected; PLT, transfusion of packed platelets.
[a]Duration of carbamazepine treatment until thrombocytopenia developed.
[b]Lowest platelet counts.
[c]Our patient.

count of 2.0×10^9/l with a normal differential count. Coagulation studies showed normal findings. A bone marrow aspirate showed increased numbers of immature megakaryocytes. Myeloid and erythroid cells were normal in number and morphology. The serum CBZ concentration was 3.5 mg/l, and the C-reactive protein (CRP) level was 33 mg/l. Hepatic and renal function test results were normal. No antinuclear antibodies, rheumatoid factor, or platelet-associated IgG (PAIgG) was detected. The patient was treated with prednisolone (1 mg/kg/day) and CBZ was discontinued immediately. Numbers of platelets and white blood cells returned to normal 7 days later. To confirm the etiology of thrombocytopenia, we attempted a challenge test with reintroduction of CBZ. For this investigation, we obtained approval from the institutional committee for human rights and fully informed consent from the patient and his parents.

METHODS

A challenge test was carried out by a single oral administration of 2.3 mg/kg (100 mg) of CBZ. We sequentially measured complete blood counts, serum levels of CRP and interleukin (IL)-6, and PAIgG values. Serum IL-6 levels were assessed using a commercially available enzyme-linked immunosorbent assay kit (Immunotech, Marseille, France). This ELISA system specifically detected human IL-6, and its detection limit was 3.9 pg/ml. In addition, we examined plasma antibodies against CBZ-conjugated platelet glycoproteins (GP) IIb/IIIa and Ib. The antibodies to the GP were quantified by an antigen-capture enzyme-linked immunosorbent assay as reported previously [17]. Briefly, platelets obtained from a normal adult volunteer were incubated with phosphate-buffered saline with or without CBZ. They then were exposed to the patient's serum (final dilution 1:10). The platelets were then washed, lysed, and ultracentrifugated. The supernatant was dispensed into plastic plates precoated with monoclonal antibodies against GP IIb/IIIa or Ib. GP-bound IgG was sandwiched with biotinated anti-IgG monoclonal antibody; the signal was accentuated by an avidin-biotin-peroxidase system.

RESULTS OF CHALLENGE TEST

After CBZ administration, the patient manifested a sequence of changes (Table II). Fever, cutaneous flushing, and conjunctival hyperemia occurred at 4 hr. Leukocyte counts increased to 12.2×10^9/l with a left shift in the neutrophilic series at 4 hr. On the first day, serum CRP levels rose to 43 mg/l, serum IL-6 levels increased to 16.3 pg/ml, and PAIgG was detected (90.2 ng/10^7 cells). On the second day, platelet counts decreased to 57×10^9/l and eosinophils increased to 0.36×10^9/l. No antibodies against platelet glycoprotein IIb/IIIa or Ib were detected in plasma. All abnormal laboratory values returned to prechallenge levels about 1 week later. Bone marrow examination on day 8 showed an abnormal in-

TABLE II. Chronology of Laboratory Data Following Challenge With Carbamazepine*

		Postchallenge	Days				
	Prechallenge	4 hr	1	2	3	5	8
Platelets ($\times 10^9$/1)	411	111	73	57	72	99	226
Leukocytes ($\times 10^9$/1)	5.5	12.2	12.8	4.0	3.7	4.0	5.4
Eosinophils (%)	2	0	2	9	4	5	4
Band-form neutrophils	5	74	7	3	0	1	2
Segmented-form neutrophils	56	9	77	54	50	45	51
Lymphocytes	31	0	10	24	39	45	38
Monocytes	6	17	4	8	7	1	5
Hemoglobin (g/l)	146	133	128	130	123	125	135
CRP (mg/1)	0		43	29		3	1
PAIgG (ng/10^7cells)	<12.5		90.2			<12.5	
IL-6 (pg/ml)	4.3		16.3			9.7	

*Serum concentrations of carbamazepine were 4.4 mg/l 4 hr and 4.8 mg/l 1 day after administration.
CRP, C-reactive protein; PAIgG, platelet-associated IgG; IL-6, interleukin-6.

crease in eosinophils. Megakaryocytes were normal in number and morphology.

DISCUSSION

Our CBZ challenge study revealed that thrombocytopenia and eosinophilia occurred 2 days after the rapid appearance of fever, flushing, conjunctival hyperemia, and leukocytosis with a left shift of neutrophils. In addition, serum concentrations of CRP and IL-6 increased. PAIgG, not detectable on admission, was demonstrated on the first day of the challenge test. These abnormal findings normalized about 1 week later. This report is the first description of CBZ-induced thrombocytopenia including definition by a challenge test, although a number of occurrences of thrombocytopenia have been reported.

The pathophysiologic mechanism of CBZ-induced thrombocytopenia remains unknown. An immune mechanism has been proposed for thrombocytopenia, as CBZ-dependent antiplatelet antibodies have been identified [4]. In contrast, no plasma antibodies against platelet GP IIb/IIIa or Ib in the presence or absence of CBZ were found in our study. Drug-specific T-cell clones can be found in the blood of patients with skin reactions and other inflammatory responses [18,19]. The patients were allergic to many types of medicines including CBZ, penicillins, sulphonamides, lidocaine, and phenytoin [19]. Most drug-specific T-cell clones express the $\alpha\beta$ type of T-cell receptor, show the $CD4^+$ or $CD8^+$ phenotype, and are major compatibility complex class I or II restricted [18,19]. Activated T cells are presumed to release proinflammatory cytokines upon drug allergy [19]. In our patient, the laboratory abnormalities suggest that CBZ caused an inflammatory reaction within hours. A proinflammatory cytokine which showed elevation, IL-6, can directly stimulate megakaryocytopoiesis and platelet production [20]. Reactive thrombocytosis in inflammatory disorders has been postulated to result from elevation of IL-6 [20]. The high levels of serum IL-6 occurring in the CBZ challenge test may represent a compensatory effect in CBZ-induced thrombocytopenia. Although the antecedent increase in PAIgG levels may be involved in the thrombocytopenia, we found no definite evidence for an immune-mediated mechanism. To reveal the mechanism of CBZ-induced thrombocytopenia, further studies are required.

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